

AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0005] with the following amended paragraph:

[0005] *Conus* is a genus of predatory marine gastropods (snails) which envenomate their prey. Venomous cone snails use a highly developed projectile apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as *Conus magus* the cone detects the presence of the fish using chemosensors in its siphon and when close enough extends its proboscis and fires a hollow harpoon-like tooth containing venom into the fish. This immobilizes the fish and enables the cone snail to wind it into its mouth via an attached filament. ~~For general information on *Conus* and their venom see the website address~~ <http://grimwade.biochem.unimelb.edu.au/cone/reference.html>. Prey capture is accomplished through a sophisticated arsenal of peptides which target specific ion channel and receptor subtypes. Each *Conus* species venom appears to contain a unique set of 50-200 peptides. The composition of the venom differs greatly between species and between individual snails within each species, each optimally evolved to paralyse its prey. The active components of the venom are small peptides toxins, typically 10-40 amino acid residues in length and are typically highly constrained peptides due to their high density of disulphide bonds.

Please replace paragraph [0006] with the following amended paragraph:

[0006] The venoms consist of a large number of different peptide components that when separated exhibit a range of biological activities: when injected into mice they elicit a range of physiological responses from shaking to depression. The paralytic components of the venom that have been the focus of recent investigation are the α -, ω - and μ -conotoxins. All of these conotoxins act by preventing neuronal communication, but each targets a different aspect of the process to achieve this. The α -conotoxins target nicotinic ligand gated channels, the μ -conotoxins target the voltage-gated sodium channels and the ω -conotoxins target the voltage-gated calcium channels (Olivera et al., 1985; Olivera et al., 1990). For example a linkage has been established between α -,

~~α A- & ϕ -conotoxins~~ ψ -conotoxins and the nicotinic ligand-gated ion channel; ω -conotoxins and the voltage-gated calcium channel; μ -conotoxins and the voltage-gated sodium channel; δ -conotoxins and the voltage-gated sodium channel; κ -conotoxins and the voltage-gated potassium channel; conantokins and the ligand-gated glutamate (NMDA) channel.

Please replace paragraph [0015] with the following amended paragraph:

[0015] Examples of synthetic aromatic amino acid include, but are not limited to, nitro-Phe, 4-substituted-Phe wherein the substituent is C₁-C₃ alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO₃H and -NHAc. Examples of synthetic hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of synthetic basic amino acids include, but are not limited to, N-1-(2-pyrazolanyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolinanyl]-Gly and 2-[3-(2S)pyrrolinanyl]-Ala. These and other synthetic basic amino acids, synthetic hydroxy containing amino acids or synthetic aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; ~~see also <http://www.amino-acids.com>~~), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA. Examples of synthetic acid amino acids include those derivatives bearing acidic functionality, including carboxyl, phosphate, sulfonate and synthetic tetrazolyl derivatives such as described by Ornstein et al. (1993) and in U.S. Patent No. 5,331,001, each incorporated herein by reference.

Please replace paragraph [0101] with the following amended paragraph:

[0101] μ -Conopeptide S3.2 was tested for activity on sodium channels as follows. S3.2 was administered to mice by intracerebroventricular (ICV) injection. Administration of S3.2 in this manner caused mice to show a spectrum of activity that is characteristic of all sodium channel blockers, including ~~rapid~~ rapid loss of righting reflex, coma-like inactivity and spastic uncontrolled

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limb movement. Following intrathecal (it) administration to mice, S3.2 causes rapid hindlimb paralysis that spreads to include the entire body over a course of 10-20 minutes followed by death, presumably due to respiratory paralysis. However, unlike classic μ -conopeptides, S3.2 has no significant activity following intravenous administration (iv) to mice. Classic μ -conopeptides, such as GIIIA and PIIIA, cause rapid paralysis and death following iv administration, indicating their activity at skeletal muscle sodium channels. To confirm the selectivity of S3.2, 80 nmol was administered iv to rats. The effect of S3.2 was measured on skeletal muscle contraction, blood pressure and heart rate. S3.2 was found to have no effect on any of these parameters. Controls were performed using classical μ -conopeptides, including Sm3.1, Sm3.3 and Bu3.1 described herein, also administered iv at 80 nmol. These control peptides caused a dramatic decrease in skeletal muscle contractility, as well as a significant drop in systemic blood pressure. Thus, μ -conopeptide S3.2 surprisingly is selective for neuronal sodium channels. The most obvious difference between the S3.2 sequence and the sequences of these other peptides is a shortened first loop (the first loop between cysteine residues) which lacks a charged amino acid.